Brain Damage in the Infant—Genetic Aspects

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• **With better control of environmental agents in malformation and brain damage in infants, increasing attention is being given to genetic factors as causes of brain damage. An example of such a hereditary condition is Tay-Sachs disease, which leads to degeneration of nerve cells in the brain, resulting in mental deterioration, blindness and early death. Genetic factors are readily traceable in this condition. But in many other cases of brain damage, it is more difficult to decide whether a hereditary cause exists, whether an unfavorable environment was responsible, or whether factors in the heredity and environment acted together.**

The recognition of the importance of genetic factors in brain damage to the infant as well as in other congenital malformations is a first step in the direction of prevention. Our position at this time may be compared to that of medical science when Pasteur and Koch demonstrated the importance of microorganisms in the pathogenesis of infectious diseases; it took decades for those diseases to be truly effectively combated and it may take a long time to learn how to keep a potentially dangerous genotype in the embryo from becoming manifest.

THE MORE SUCCESSFUL that modern medical methods are in diminishing or eliminating environmental agents as causes of disease, the more is the recognition given to the importance of genetic factors. When it was found that rickets is due to vitamin D deficiency, it seemed to be removed from the defects that have a genetic basis. But when vitamin D prophylaxis and therapy were applied on a large scale, some cases of rickets proved highly resistant;[1] and it was then discovered that specific genes exist which are responsible for the disease in persons supplied with normally adequate doses of the vitamin.[12] A similar situation exists with regard to brain damage in infants. The more we can eliminate the effect of nongenetic agents, acting prenatally or at birth, the greater will be the relative weight of genetic factors.

In many cases it is not possible to tell with certainty whether brain damage is caused by genetic or by nongenetic interference with normal development. Heredity and environment are not mutually exclusive entities but interact in the production of a normal or abnormal organism. Brain damage of some types may be produced in any individual if circumstances are unfavorable—say, severe mechanical harm or severe anoxia at birth. Other kinds will originate under the best constellation of prenatal or perinatal factors, for example the abnormal storage of lipoids in cells of the central nervous system characteristic of Tay-Sachs disease. Between these extremes lie many cases in which genetic predispositions are expressed under some sets of conditions and remain unexpressed in others.

How can one recognize the presence of genetic factors in brain damage? The clearest evidence is provided by simple recessive condition. Infantile amaurotic idiocy (Tay-Sachs disease) may serve as an example.[7] The parents of the affected infants are always normal. If one pools the data for children from different parents, one obtains the classical Mendelian ratio of three normal to one affected (granted the necessary corrections for the existence of some families which by chance did not contain a single affected child although the expectation for affected children was one in four.) This situation is explained by the presence in each parent of a dominant gene for normality and a recessive gene for the disease. Among the children, one quarter will receive an abnormal gene from each parent and, being homozygous, will be affected.

Two additional facts lend support to this theory of genetic causation of Tay-Sachs disease, namely, the absence of affected children in other sibships of the family group and the high incidence of consanguinity among the parents of affected children. Since the recessive gene is a rare one, most persons who carry it would marry spouses free from it and therefore have normal children only. Even though many normal relatives of the affected children would carry the recessive gene, their marriages are not likely to lead to Tay-Sachs offspring. The genetic interpretation thus is compatible with the fact, and even requires it, that a sibship with affected children usually stands alone among a multitude of normal relatives, in earlier and later generations, in the direct line of descent, and in collaterals.

Occasionally, of course, a normal carrier of the abnormal gene, perhaps a sib of one who is affected, will marry someone who is also a carrier. Then the trait will appear in successive generations. This will be particularly so if the spouses are closely related to each other by descent. Then they may carry the

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same abnormal gene derived from their common ancestor. Genetic causation of a defect, based on a rare recessive gene, should be reflected in relatively frequent consanguinity of the parents of affected children. Indeed, in data on Tay-Sachs disease, the consanguinity rates of the parents were from 20 to over 50 per cent, in contrast to the rates in most general populations which lie between 0.1 and 1 per cent.

Considering the smallness of modern families, a disease such as Tay-Sachs with its chance of presence in only one quarter of the children, will usually appear in a single child only. The so-called sporadic outcropping of an affected child, which seems to contradict a naive view of inheritance, is thus a necessary aspect of a theory of inheritance which focuses attention on inherited genes and not on individually expressed phenotypes.

What has been discussed for amaurotic idiocy is nearly equally valid for phenylketonuria.[8] Here, a homozygous recessive gene causes abnormal metabolism of phenylalanine which leads to brain damage with resulting mental deficiency. But there is some variability in amount of excretion of phenylpyruvic acid and an occasional affected individual may approach average mental capacities.

Geneticists use a descriptive phrase for such occurrences. They speak of "incomplete manifestation" of the genotype or of "incomplete penetrance." No more is implied with these words than that the effectiveness of the genes to produce a certain trait may not be absolute. The causes for the absence of a trait in spite of the presence of the genes which usually lead to its appearance may be manifold. A given gene pair does not work by itself. It is only one agent among thousands of other genes whose collaboration makes possible development and functioning. If the genes for phenylketonuria find themselves in the "genetic background" of individual *A*, they may produce a stronger effect than if they are in the different genetic background of individual *B*. And if the genetic background can influence the expression of a specific gene pair, then, equally, the environment, prenatal or postnatal, may have its part in the manifestation of the gene pair. Indeed, the recent beginnings of feeding phenylketonuric infants with diets low in phenylalanine are an attempt to suppress the penetrance of the abnormal genotype by therapeutic environmental means.

The few atypical phenylketonuric persons do not seriously disturb the picture of clear genetic determination of the defect. As in Tay-Sachs disease, the parents are normal, the corrected ratio of normal to affected children is 3:1, the affected sibship usually stands alone in the family group, and consanguinity of the parents is frequent. And an additional fact proves the genetic causation. Tolerance tests for phenylalanine given to the parents, or to the normal sibs of the patients demonstrate a mean difference between the normal but heterozygous carriers of a single gene for phenylketonuria and the majority of normal individuals who are not carriers.[5]

The problems of recognizing genetic determination of defects are more complex when incomplete penetrance often results in individuals who carry a certain genotype but do not manifest the trait associated with it. Most frequent among the infantile defects of the central nervous system are anencephaly, hydrocephaly and spina bifida. Jointly, they are responsible for more than five deaths and stillbirths per 1,000 newborn. To some degree they seem to belong together: The association in one infant of anencephaly with spina bifida is more than 30 times as frequent as would be expected by chance and hydrocephaly with spina bifida more than 150 times.[9] Are these defects to the brain or other parts of the central nervous system caused by some simple genetic situation in the embryo which may express itself in variable ways? Or are they the result of damage from extra-embryonic sources, either provided by the mother or mediated by her? Or, finally, are they developmental derailments due to nongenetic, chance mishaps within the embryo?

Some light on these questions is shed by the finding that in a large British sample the frequency of the malformations among the sibs of affected infants was more than six times higher than in a control population. This rules out an interpretation of these malformations as the result of accidental developmental disorders. But it is compatible either with the interpretation that the prenatal environment provided by a specific woman may be repeatedly unfavorable, or that genetic factors common to many sibs are responsible. To decide between these alternatives, students have considered a variety of external variables which conceivably might be concerned with the origin of early brain damage as represented by anencephaly and related defects. No correlations of frequency of defects were apparent with diseases of the mother, with various socioeconomic indices, nor probably with maternal age. In the British sample, there was a higher risk at the first pregnancy than at the following ones, except for a rise after the sixth. Since the genetic constitution of sibs is independent of parity, the parity effect shows that some nongenetic factors pay a role in the causation of these defects of the central nervous system but they do not seem sufficient to account for the relatively high "repeat frequencies" of defectives in sibships in which an affected child has appeared.

Suggestions of genetic determination come from the fact that there is a slightly increased frequency over control groups of defects among the more distant relatives of parents of defective children. And finally, there is the greatly increased rate of early abortion in sibships in which infants had been affected by one or more of the three defects. This high rate of abortion has been interpreted as being caused by the loss of particularly severely affected embryos.

From a Swedish study it was concluded that anencephaly is due to a single recessive gene (perhaps a different one in different families) whose expression varies from usually causing early abortion to, more rarely, anencephalic development until term.[3] One might add that the presence of the postulated genotype may sometimes be compatible with perfectly normal development. Such a hypothesis is intrinsically fully acceptable. Presumably, anencephaly is initiated at a very early embryonic stage, namely, at the time when lateral folds of the medullary plate rise and meet each other, thus enclosing the brain. Given some variability in these processes they may fail to occur all along the length of the neural plate and result in early abortion; may lead to partial closure with anencephaly with or without spina bifida; may permit the normal development of the brain but cause more or less extensive spina bifida; or may permit complete closure all along the system and the birth of a nondefective infant. Of course, the acceptability of such an interpretation does not mean that it is correct, and a recent study in a Japanese sample has failed to reveal high abortion rates in mothers of anencephalics.[10]

Even if a genetic interpretation is valid in many instances, it must be kept in mind that one and the same defect may owe its appearance to abnormal genes in one case and to abnormal environmental circumstances in another. It has been established by numerous animal experiments that well-known genetic defects can be produced artificially as "phenocopies."[11] This is not surprising, since the chain of normal developmental events may be interrupted or diverted as readily by abnormal gene substitutions which can block or modify biochemical reactions as by abnormal external agents which can block or modify the same reactions. Moreover, the same abnormal end result can be produced by a gene affecting step X in the chain of events or by a nongenetic agent affecting an earlier or later step Y in the same chain.

These facts should keep us from being dogmatic in too readily assigning either genetic or nongenetic factors to the origin of a brain damage of a given type. And even apart from interaction between gene and environment, the same kind of effect can often be produced by different genes, in different ways, or by different external agents, in different ways. In the fruitfly *Drosophila*, many tens of different genes are known which disturb the normal development of the brain or of the peripheral nervous system. Some are dominant, others recessive; some are fully penetrant, others incompletely so; some are in the X chromosome, others in one or the other autosome. Developmentally the effects of these genes may appear alike or different, and biochemically each one seems specifically different. In other examples, an organ may be defective because it never developed completely after a certain stage, or it may be defective because, having developed well, it then begins to degenerate.

What is true of different genic causes is equally true of extraneous ones. Brain defects may be induced by chemical agents acting during the earliest initial stages of organogenesis, as was proven many years ago on the eggs of fishes and frogs. An example of reversal of early normality was recently demonstrated in the chicken. If hens are fed with selenium, the brain, spinal cord, eyes and limb buds of the embryos in their eggs first develop normally. Later, however, necrosis sets in within certain areas of these organs and causes defects in them as well as, secondarily, in nearby areas.[4] These and other observations have shown the early optimism to be premature that the artificial production of phenocopies would lead to the discovery of "the" point of attack on abnormal development by a gene with a similar final effect.

At the time the present discussion was presented before the California Medical Association, one of the supposedly most striking examples of an interaction of genetic and nongenetic agents in causing abnormal development of the brain was mongolism. The very great rise in the risk of mongolian births from women in the later period of their reproductive life seemed evidence for environmental, intra-uterine interference with normal brain differentiation. It was clear, however, that genetic factors play an important part in the etiology of mongolism since a mongolian nonidentical twin is nearly always associated with a normal twin sib while a mongolian identical twin probably always has a mongolian cotwin. This would be expected if a specific genetic constitution is a prerequisite for mongolism, since two identical twins carry the same genes and two non-identical twins different genes.

Recent discoveries, in France, England, Sweden and elsewhere, have furnished dramatic proof of the genetic determination of mongolism and, at the same time, seem to have removed intra-uterine variability as a cooperating agent in the causation of this condition. Mongols have been shown to possess 47, instead of the typical 46 chromosomes in their cells: One of the smallest of the human chromo-

somes occurs three times instead of the normal two-fold representation. The age effect of the mother which leads to mongolism is not exerted on the developing embryo, but on the nucleus of the egg before it is ready for fusion with the sperm nucleus. Apparently the process of "nondisjunction" in oogenesis—long known in experimental organisms—occurs relatively frequently in older women and results in the retention of two chromosomes of a given pair in the egg nucleus instead of normal segregation which retains only one. Mongolism is due to abnormal development caused by the abnormal "unbalanced" genetic-chromosomal constitution.

An interaction between specific genotypes and specific environments has been demonstrated experimentally between genotypes and excessively reduced atmospheric pressure in the production of skeletal malformations in the mouse.[6] In five different strains, for 0 to 29 per cent of the young from unexposed control mothers showed deviations from a standard type of sternum. Reduced atmospheric pressure, equivalent to an altitude of 29,000 feet, applied to pregnant females resulted in from over 20 to over 70 per cent deviations from the norm. The five strains differed in the spontaneous incidence of deviations as well as in the frequency of induced variants. Moreover, the strain with the highest frequency of induced variants had a lower frequency of spontaneous ones than some of the other strains.

The existence of genetic factors in brain damage poses the problems of counseling to parents and relatives of affected children. If the genetic situation is simple, such counseling can be given in specific terms. If it is complex, or unclear, the best that can be done is in reference to empirical risk figures, obtained from large representative samples. Some such surveys contain significant information like those on anencephaly and related defects, as discussed herein. For other traits, only limited data are available. It can be expected that new detailed studies of populations will enable the counselor to increase the precision of his predictions.

The recognition of the importance of genetic factors in brain damage as well as in other congenital malformations is a first step in the direction of their prevention. Our position at this time may be compared to that of medical science when Pasteur and Koch demonstrated the importance of microorganisms in the pathogenesis of infectious diseases. It was decades before these diseases were truly effectively combated and it may take a long time for us to know how to keep a potentially dangerous genotype in the embryo from becoming manifest. The recognition of genetic causes of maldevelopment is not an endpoint but rather a preparation for future action.

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